Remarks

Applicant has carefully reviewed this Application in light of the Office Action sent 17 December 2007. To expedite issuance of a patent from this Application, Applicant has amended Claims 1, 11, 21-22, 25, 27, and 29-31. Applicant respectfully requests reconsideration and allowance of all pending claims.

Claims 21-22, 25, 27, and 29-30 Recite Patentable Subject Matter
Under 35 U.S.C. § 101

The Examiner rejects Claims 21-22, 25, 27, and 29-30 as being directed to nonstatutory subject matter. Specifically, the Examiner states:

> Claims 21,22, 25, 27, 29, and 30 are drawn to logic encoded in one or more media. A review of the specification does not show a definition of computer readable media such that the claimed subject matter excludes an embodiment that is information on a carrier wave. As such an embodiment of the claims reads on non-statutory subject matter.

> Claims 21, 22, 25, 27, 29, and 30 are drawn to logic encoded in one or more media. The claims do not have a limitation that the information is a computer program on computer readable media or that the information comprises computer executable instructions on computer readable media. As such the claimed subject matter includes an embodiment of non-computer executable instructions such as a scientific paper dealing with the claim subject matter. As such an embodiment reads on literature which is non-statutory subject matter.

Although Applicant does not necessarily agree with the Examiner, to expedite issuance of a patent from this Application, Applicant has amended Claims 21-22, 25, 27, and 29-30. Applicant respectfully requests reconsideration and allowance of Claims 21-22, 25, 27, and 29-30.

The Claims Recite Patentable Subject Matter
Under 35 U.S.C. § 101

The Examiner rejects Claims 1-2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 under 35 U.S.C. § 101 as being directed to nonstatutory subject matter. Specifically, the Examiner states:

> Claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 do not require production of a tangible result in a form that is useful to the user of the process or apparatus. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical form, or in a user readable format, or by including a result that is a physical transformation.

Although Applicant does not necessarily agree with the Examiner, to expedite issuance of a patent from this Application, Applicant has amended independent Claims 1, 11, 21, and 31. Applicant respectfully requests reconsideration and allowance of independent Claims 1, 11, 21, and 31 and all their dependent claims.

Claims 19-20 are Definite Under 35 U.S.C. § 112

The Examiner states:

> Claim 19 and dependent claim 20 recite the limitation "The method of claim 5" and "the first set of empirically derived minimum binding-energy distances or second sets of empirically derived minimum binding-energy distances and well-depth values". There is insufficient antecedent basis for these limitations in the claim. The applicants may have intended that claim 19 was dependent on claim 15. For the purpose of examination claim 19 has been interpreted to depend on claim 15.

Applicant has amended dependent Claim 19. Applicant respectfully requests reconsideration and allowance of dependent Claims 19-20.

The Claims are Definite Under 35 U.S.C. § 112

The Examiner rejects Claims 1-2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 under 35 U.S.C. § 112 para. 2 as being indefinite. Specifically, the Examiner states:

> Claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 are indefinite for recitation in independent claims 1, 11, 21, and 31 of the phrase "calculate a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair" because the PMF is a parameter affected by attraction as well as repulsion forces.

Applicant respectfully disagrees with the Examiner. According to the M.P.E.P., "[t]he test for definiteness under 35 U.S.C. 112, second paragraph, is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.'" M.P.E.P. ch. 2173.02 (Rev. 5, Aug. 2006). "[T]he examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement." *Id.* The M.P.E.P. states:

> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Id. "Breadth of a claim is not to be equated with indefiniteness. If the scope of the subject matter embraced by the claims is clear . . . then the claims comply with 35 U.S.C. 112, second paragraph." M.P.E.P. ch. 2173.04 (Rev. 5, Aug. 2006).

Independent Claim 1 of this Application recites:

> An apparatus comprising:
> one or more processors; and

a memory coupled to the processors comprising one or more instructions, the processors operable when executing the instructions to:

determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex;

calculate a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type;

calculate a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair;

calculate a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex; and

communicate the PMF score for presentation to a user.

Independent Claims 11, 21, and 31 recite similar limitations.

Applicant respectfully submits independent Claim 1 need not recite what additional information, if any, *calculating a potential of mean force (PMF) of the protein-ligand atom pair*, as independent Claim 1 recites, takes into account besides *the calculated repulsion term of the protein-ligand atom pair*, as independent Claim 1 recites, to clearly delineate the scope of independent Claim 1. If the other limitations of independent Claim 1 were met, *calculating a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair*, as independent Claim 1 recites, regardless of what other information, if any, were taken into account, would clearly constitute infringement. Therefore, independent Claim 1 fully "serves the notice function required by 35 U.S.C. 112, second paragraph."

The Specification provides the following description:

PMFs of protein-ligand atom pairs are derived from application of one or more atom-pair distribution functions to data that describes analyzed protein-ligand complexes, such as data from the BROOKHAVEN PROTEIN DATA BANK (PDB) or the PDB maintained by the RESEARCH COLLABORATORY FOR STRUCTURAL BIOINFORMATCIS (RCSB). As an example and not by way of limitation, in particular embodiments:

$$A_{ij} = -k_B T \ln\left[f^j_{vol\_corr}(r) \frac{\rho^{ij}_{seg}(r)}{\rho^{ij}_{bulk}} \right] = -k_B T \ln \rho^{ij}_{seg}(r) - k_B T \ln f^j_{vol\_corr}(r) + k_B T \ln \rho^{ij}_{bulk}$$

k_B is a Boltzmann factor, T is absolute temperature, $f^j_{vol\_corr}(r)$ is a ligand volume-correction factor, and ρ^{ij}_{bulk} is a number density of atom-pair type ij occurrences at a certain distance. In particular embodiments, to account for short-distance interaction between two atoms in a protein-ligand atom pair, a repulsion term is used to calculate a PMF of the protein-ligand atom pair. As an example and not by way of limitation, in particular embodiments, if two atoms in a protein-ligand atom pair of atom-pair type ij are separated from each other by a distance that is shorter than the longest distance without an occurrence of atom-pair type ij in data that describes analyzed protein-ligand complexes, a repulsion term is incorporated into the above formula. In particular embodiments, if short-distance interaction between two atoms in a protein-ligand atom pair is greater than 4 kcal/mol, the above formula is replaced by a repulsion term.

(Page 6, Line 22, through Page 7, Line 14).

Moreover, according to the M.P.E.P., if the Examiner concludes a rejection under 35 U.S.C. § 112 para. 2 is appropriate, the Examiner should provide "an analysis as to why the phrase(s) used in the claim is 'vague and indefinite.'" M.P.E.P. ch. 2173.02 (Rev. 5, Aug. 2006). Applicant respectfully submits the Examiner has provided no such analysis. Instead, the Examiner merely asserts *calculating a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair*, as independent Claims 1, 11, 21, and 31 recite, is indefinite because "the PMF is a parameter affected by attraction as well as repulsion forces." The Examiner fails to explain why the fact that "the PMF is a parameter affected by attraction as well as repulsion forces," if true, would render *calculating a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair*, as independent Claims 1, 11, 21, and 31 recite, indefinite. Should the Examiner maintain the rejection of the claims under 35 U.S.C. § 112 para. 2, Applicant respectfully requests the Examiner to provide such explanation, as directed by the M.P.E.P.

Applicant respectfully requests reconsideration and allowance of independent Claims 1, 11, 21, and 31 and all their dependent claims.

Independent Claims 1, 11, 21, and 31 are Allowable Over *Muegge I*

The Examiner rejects independent Claims 1, 11, 21, and 31 under 35 U.S.C. § 102(b) as being anticipated by Ingo Muegge et al., *Evaluation of PMF Scoring in Docking Weak Ligands to the FK506 Binding Protein*, J. MED. CHEM., Vol. 42, Pages 2498-503, 1999 ("*Muegge I*").

Applicant respectfully disagrees with the Examiner. *Muegge I* merely discloses implementing a PMF scoring function into the DOCK4 program. (Page 2499). The implementation of *Muegge I* adds van der Waals (VDW) interactions to a PMF between two atoms to assign more meaningful interaction potentials for short distances between the atoms. (Page 2499).

In contrast, independent Claim 1 of this Application recites:

> An apparatus comprising:
> one or more processors; and
> a memory coupled to the processors comprising one or more instructions, the processors operable when executing the instructions to:
>> determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex;
>> calculate a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type;
>> calculate a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair;
>> calculate a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex; and
>> communicate the PMF score for presentation to a user.

Independent Claims 11, 21, and 31 recite similar limitations.

Muegge I fails to disclose, teach, or suggest each and every limitation of independent Claim 1. As an example, *Muegge I* fails to disclose, teach, or suggest *calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type*, as independent Claim 1 recites. As discussed above, *Muegge I* merely adds VDW interactions to a PMF between two atoms to assign more meaningful interaction potentials for short distances between the atoms. Even assuming for the sake of argument the VDW interactions in *Muegge I* could properly be considered *a minimum binding-energy distance value*, as independent Claim 1 recites, *Muegge I* would still fail to disclose, teach, or suggest *calculating a repulsion term of the protein-ligand atom pair according to* the VDW interactions in *Muegge I and a well-depth value of the atom-pair type*, as independent Claim 1 recites. Nowhere does *Muegge I* even suggest the use of *a well-depth value of the atom-pair type*, as independent Claim 1 recites, to *calculate a repulsion term of the protein-ligand atom pair*, as independent Claim 1 recites. Moreover, because *Muegge I* fails to disclose, teach, or suggest *calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type*, as independent Claim 1 recites, *Muegge I* also necessarily fails to disclose, teach, or suggest *calculating a PMF of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair*, as independent Claim 1 further recites.

"To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim." *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); M.P.E.P. ch. 2131 (Rev. 3, Aug. 2005) (quoting *Verdegaal*, 814 F.2d at 631). Moreover, "[t]he identical invention must be shown in as complete detail as is contained in the patent claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989); M.P.E.P. ch. 2131 (Rev. 3, Aug. 2005) (quoting *Richardson*, 868 F.2d at 1236). Furthermore, "[t]he elements must be arranged as required by the claim." M.P.E.P. ch. 2131 (Rev. 3, Aug. 2005) (citing *In re Bond*, 910 F.2d 831, 832, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir.

1990)). As shown above, *Muegge I* fails to disclose, either expressly or inherently, each and every limitation of independent Claim 1. Therefore, *Muegge I* does not anticipate independent Claim 1 under governing Federal Circuit case law and the M.P.E.P.

For at least these reasons, independent Claims 1, 11, 21, and 31 are allowable over *Muegge I*. Applicant respectfully requests reconsideration and allowance of independent Claims 1, 11, 21, and 31 and all their dependent claims.

Independent Claims 1, 11, 21, and 31 are Allowable Over the Proposed *Muegge I-Mitchell* Combination

The Examiner also rejects independent Claims 1, 11, 21, and 31 under 35 U.S.C. § 103(a) as being unpatentable over *Muegge I* in view of John B. O. Mitchell et al., *Bleep—Potential of Mean Force Describing Protein-Ligand Interactions: I. Generating Potential*, JOURNAL OF COMPUTATIONAL CHEMISTRY, Vol. 20, No. 11, Pages 1165-76, 1999 ("*Mitchell*").

Applicant respectfully disagrees with the Examiner. As discussed above, *Muegge I* at a minimum fails to disclose, teach, or suggest *calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type*, as independent Claim 1 recites. *Mitchell* fails to make up for this deficiency of *Muegge I*, and the Examiner does not assert otherwise. The Examiner merely states, "Mitchell et al. shows in the abstract and throughout a method and apparatus for calculation of a PMF score of a protein ligand complex by determining the PMF of each atom pair of the complex. Mitchell et al. shows use of data from the Brookhaven Protein Databank . . . to aid in determining PMF of atom pairs of interest." Even assuming for the sake of argument this were true, *Mitchell* would still fail to disclose, teach, or suggest *calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type*, as independent Claim 1 recites.

The Examiner may not disregard specific recitations of Applicant's claims to maintain a rejection under 35 U.S.C. § 103(a). According to the M.P.E.P., "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. . . . Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. ch. 2143 (Rev. 5, Aug. 2006) (emphasis added). Moreover, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. All words in a claim must be considered in judging the patent ability of that claim against the prior art." M.P.E.P. ch. 2143.03 (Rev. 5, Aug. 2006) (emphasis added). As shown above, even assuming for the sake of argument the proposed *Muegge I-Mitchell* combination were proper, the proposed *Muegge I-Mitchell* combination would still fail to disclose, teach, or suggest all the limitations of independent Claim 1. Therefore, the proposed *Muegge I-Mitchell* combination does not render independent Claim 1 obvious.

Moreover, *Muegge I* tends to teach away from its proposed combination with *Mitchell*. The implementation of *Muegge I* precomputes a PMF score for a fixed protein on a grid, which speeds up the computation compared to the continuous evaluation of pair potentials for all protein-ligand atom pairs. (*Muegge I*, Page 2499). In contrast, according to the Examiner, *Mitchell* determines the PMF of each atom pair of the complex.

For at least these reasons, independent Claims 1, 11, 21, and 31 are allowable over the proposed *Muegge I-Mitchell* combination. Applicant respectfully requests reconsideration and allowance of independent Claims 1, 11, 21, and 31 and all their dependent claims.

Independent Claims 1, 11, 21, and 31 are Allowable Over the Proposed *Muegge I-Mitchell-Muegge II* Combination

The Examiner also rejects independent Claims 1, 11, 21, and 31 under 35 U.S.C. § 103(a) as being unpatentable over *Muegge I* in view of *Mitchell* and in further view of Ingo Muegge, *The Effect of Small Changes in Protein Structure on Predicted Binding Modes of Known*

Inhibitors of Influenza Virus Neuraminidase; PMF Scoring in DOCK4, MED. CHEM. RES., 9:7/8, Pages 490-500, 1999 ("*Muegge II*").

Applicant respectfully disagrees with the Examiner. As discussed above, *Muegge I* and *Mitchell* at a minimum fail to disclose, teach, or suggest **calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type**, as independent Claim 1 recites. *Muegge II* fails to make up for this deficiency of *Muegge I and Mitchell*, and the Examiner does not assert otherwise. The Examiner merely states, "Muegge shows comparison of root mean square deviations of multiple ligands on pages 492-497." Even assuming for the sake of argument this were true, *Muegge II* would still fail to disclose, teach, or suggest **calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type**, as independent Claim 1 recites.

The Examiner may not disregard specific recitations of Applicant's claims to maintain a rejection under 35 U.S.C. § 103(a). As shown above, even assuming for the sake of argument the proposed *Muegge I-Mitchell-Muegge II* combination were proper, the proposed *Muegge I-Mitchell-Muegge II* combination would still fail to disclose, teach, or suggest all the limitations of independent Claim 1. Therefore, the proposed *Muegge I-Mitchell-Muegge II* combination does not render independent Claim 1 obvious.

For at least these reasons, independent Claims 1, 11, 21, and 31 are allowable over the proposed *Muegge I-Mitchell-Muegge II* combination. Applicant respectfully requests reconsideration and allowance of independent Claims 1, 11, 21, and 31 and all their dependent claims.

**Independent Claims 1, 11, 21, and 31 are Allowable Over the
Proposed *Muegge I-Mitchell-Morris* Combination**

The Examiner also rejects independent Claims 1, 11, 21, and 31 under 35 U.S.C. § 103(a) as being unpatentable over *Muegge I* in view of *Mitchell* and in further view of Garrett M. Morris et al., *Automated Docking Using a Lamarckian Genetic Algorithm and an Empirical Binding Free Energy Function*, JOURNAL OF COMPUTATIONAL CHEMISTRY, Vol. 19, No. 14, Pages 1639-62, 1998 ("*Morris*").

Applicant respectfully disagrees with the Examiner. As discussed above, *Muegge I* and *Mitchell* at a minimum fail to disclose, teach, or suggest *calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type*, as independent Claim 1 recites. *Morris* fails to make up for this deficiency of *Muegge I and Mitchell*, and the Examiner does not assert otherwise. The Examiner merely asserts *Morris* discloses using genetic algorithms in docking programs to predict bound conformations of flexible ligands. Even assuming for the sake of argument this were true, *Morris* would still fail to disclose, teach, or suggest *calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type*, as independent Claim 1 recites.

The Examiner may not disregard specific recitations of Applicant's claims to maintain a rejection under 35 U.S.C. § 103(a). As shown above, even assuming for the sake of argument the proposed *Muegge I-Mitchell-Morris* combination were proper, the proposed *Muegge I-Mitchell-Morris* combination would still fail to disclose, teach, or suggest all the limitations of independent Claim 1. Therefore, the proposed *Muegge I-Mitchell-Morris* combination does not render independent Claim 1 obvious.

For at least these reasons, independent Claims 1, 11, 21, and 31 are allowable over the proposed *Muegge I-Mitchell-Morris* combination. Applicant respectfully requests

reconsideration and allowance of independent Claims 1, 11, 21, and 31 and all their dependent claims.

Conclusion

For at least the foregoing reasons, Applicant respectfully requests allowance of all pending claims.

If a telephone conference would advance prosecution of this Application, Applicant invites the Examiner to call Travis W. Thomas, attorney for Applicant, at 650-739-7503.

Please charge $460.00 for a two-month extension of time to Deposit Account No. 02-0384 of BAKER BOTTS L.L.P. The Commissioner is authorized to charge any fee due and credit any overpayment to Deposit Account No. 02-0384 of BAKER BOTTS L.L.P.

Respectfully submitted,

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